

EXHIBIT A

Polymers in Drug Delivery

EDITED BY

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Andreas G. Schätzlein

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Prefac

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Drug Delivery

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1.1 DRUG I

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TABLE 4.4
pH-Sensitive Polymers Commonly Used in the Production of Delayed-Release Oral Dosage Forms

| Polymer | Dissolution Threshold pH | Aqueous Dispersion |
|--|--------------------------|--|
| Cellulose Derivatives | | |
| Cellulose acetate trimellitate | 5.0 | — |
| Hydroxypropyl methylcellulose 55 | 5.5 | — |
| Hydroxypropyl methylcellulose acetate succinate L | 5.5 | Aqcoat AS-L |
| Hydroxypropyl methylcellulose acetate succinate M | 6.0 | Aqcoat AS-M |
| Cellulose acetate phthalate | 6.0 | Aquacoat CPD |
| Hydroxypropyl methylcellulose acetate succinate H | 6.8 | Aqcoat AS-H |
| Acrylic Derivatives | | |
| Poly(methacrylic acid, ethyl acrylate) 1:1 | 5.5 | Eudragit L30-D55 Eudragit 30D Kollonut MAE30 DP Acryl-crx |
| Poly(methacrylic acid, methyl methacrylate) 1:1 | 6.0 | — |
| Poly(methacrylic acid, methyl methacrylate, methyl acrylate) 2.5:6.5:1 | 6.8 | Eudragit FS |
| Poly(methacrylic acid, methyl methacrylate) 1:2 | 7.0 | — |
| Polyvinyl Derivatives | | |
| Polyvinyl acetate phthalate | 5.0 | Suretetic |

Note: All polymers are available in powder/granule form for use in organic solutions and in some cases ready-to-use aqueous dispersions.

A polymer with a dissolution threshold pH in the range 5 to 6 is considered ideal for use as an enteric coat; this is based on the premise that the pH of the stomach, even in the fed state, will rarely reach this level but will exceed this level in the duodenum, where secretion of bicarbonate neutralizes the acidic chyme leaving the stomach.

There is no single enteric polymer that is applicable for the enteric coating of all drug molecules. The nature of the core material (acidity or basicity, or permeability through different enteric polymer films) may limit the choice of polymer. The pK_a of the coating polymer must also be carefully considered, and the potential for premature release in the stomach (for polymers with low pK_a values) weighed against the requirement for a rapid release in the small intestine. Because the physicochemical properties of the drug will have a bearing on this, it is important to consider the consequences of premature release in the stomach (drug degradation or risk of mucosal damage) alongside the requirement for a rapid release of a poorly soluble drug in the small intestine in order to optimise bioavailability and achieve the desired therapeutic effect.

Enteric coating is not without its problems. A lag time of 1.5 to 2 h postgastric emptying for complete disintegration of an enteric-coated capsule and tablet has been demonstrated [6,24]. This is slower than reported for *in vitro* disintegration times, and implies that modified-release dosage forms should be designed as multiple-unit systems, in which the increased surface-area-to-volume ratio would reduce the time for intestinal disintegration while minimizing the possibility of total failure of the dosage form and premature release in the stomach. Furthermore, the *in vivo* evidence highlights the need for new enteric polymers to be developed, which will improve the rapidity